

### ***Remarks***

#### ***I. Support for the Amendments***

Support for the forgoing amendments to the claims can be found throughout the specification. These amendments do not add new matter, and their entry and consideration are respectfully requested.

#### ***II. Status of the Claims***

By the forgoing amendments, claims 10-14 have been cancelled without prejudice or disclaimer. Applicants reserve the right to prosecute the subject matter of these claims in one or more continuing applications. Claims 4, 6, 8, 16 and 17 have been amended. Upon entry of the forgoing amendments, claims 1, 3-9 and 15-17 are pending in the application, with claims 1, 3 and 4 being the independent claims.

#### ***III. Summary of the Office Action***

In the Office Action dated June 17, 2003, the Examiner has made five rejections of and one objection to the claims. Applicants respectfully offer the following remarks to overcome or traverse each of these elements of the Office Action.

#### ***IV. The Rejection Under 35 U.S.C. § 112, First Paragraph***

In the Office Action at pages 3-5, the Examiner has rejected claim 11 under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection.

However, solely to expedite prosecution, and not in acquiescence to this rejection, claim 11 has been cancelled. Thus, the rejection to this claim under 35 U.S.C. § 112, first paragraph has been rendered moot.

***V. The Rejection Under 35 U.S.C. § 112, Second Paragraph***

In the Office Action at page 5, the Examiner has rejected claims 4, 5, 8-14, 16 and 17 under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse this rejection.

However, solely to expedite prosecution, and not in acquiescence to this rejection, claims 10-14 have been cancelled. Hence, the portion of this rejection that may have applied to these claims has been rendered moot. Applicants also respectfully traverse this rejection as it may apply to the remaining claims.

***A. The Rejection of Claims 4, 5, 16 and 17, Reciting "substantial part"***

With regard to claims 4, 5, 16 and 17, the Examiner asserts that the term "substantial part" renders to claim indefinite, as it is allegedly unclear how big the 3' UTR needs to be to function as an instability sequence. Applicants respectfully traverse this rejection.

Present claim 4 (and hence, claims 5, 16 and 17 that depend ultimately therefrom) recites a reporter gene DNA expression system comprising: 1) an expression cassette consisting of one or more genes encoding a protein having a detectable signal and 5' and 3' UTR sequences comprising operably-linked expression control elements; and 2) an instability region consisting of at least 20-100 nucleotides of the 3' UTR of a gene sequence which confers instability to a mRNA, wherein the instability region is inserted into the 3' UTR of the expression cassette. Applicants respectfully submit that present claim 4 (and

hence, the claims ultimately dependent therefrom) clearly recites that the 3' UTR needs to be at least 20-100 nucleotides to function as a an instability sequence. Applicants respectfully submit that these claims are not indefinite. In view of the forgoing remarks and amendments, reconsideration and withdrawal of this rejection are respectfully requested.

***B. The Rejection of Claims 4, 5, 8, 9, 16 and 17, Reciting "associated"***

The Examiner has next rejected claims 4, 5, 8, 9, 16 and 17, asserting that the word "associated" renders the claims indefinite. Applicants respectfully traverse this rejection.

As noted above, present claim 4 (and hence, claims 5, 8, 9, 16 and 17 that depend ultimately therefrom) recites "... 1) an expression cassette consisting of one or more genes encoding a protein having a detectable signal and 5' and 3' UTR sequences comprising operably-linked expression control elements ...". Similarly, present claim 8 recites "... (b) a control DNA expression system comprising a gene coding for expression of a second protein having a detectable signal, wherein the gene comprises DNA coding for the amino acid sequence of the protein together with 5' and 3' UTR sequences comprising operably-linked expression control elements, but lacking any functional mRNA instability sequences." Applicants respectfully submit that the present claims clearly recite 5' and 3' UTR sequences comprising operably-linked expression control elements. In view of the forgoing remarks and amendments, reconsideration and withdrawal of this rejection are respectfully requested.

***C. The Rejection of claims 16 and 17***

The Examiner has also rejected claims 16 and 17, asserting that the word "derived" renders the claims indefinite, as the metes and bounds of the claim allegedly cannot be established. Applicants respectfully traverse this rejection.

However, solely to expedite prosecution, and not in acquiescence to this rejection, the term "derived" has been removed from present claims 16 and 17. Hence, this portion of the rejection has been overcome, and reconsideration with withdrawal are respectfully requested.

***D. Summary***

In view of the forgoing amendments and remarks, Applicants respectfully submit that claims 4, 5, 8, 9, 16 and 17 are not indefinite. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, of these claims are respectfully requested.

***VI. The Rejection Under 35 U.S.C. § 102(b) Over Banholzer***

In the Office Action at page 6, the Examiner has rejected claims 4-7, 10, 12-14, 16 and 17 under 35 U.S.C. § 102(b), as being unpatentable over Banholzer *et al.* (*Mol. Cell. Biol.* 17:3254-3260 (1997); hereinafter "Banholzer"). Applicants respectfully traverse this rejection.

However, solely to expedite prosecution, and not in acquiescence to this rejection, claims 10 and 12-14 have been cancelled. Hence, the portion of this rejection that may have

applied to these claims has been rendered moot. Applicants also respectfully traverse this rejection as it may apply to the remaining claims.

The Examiner contends that Banholzer discloses three plasmid constructs pMx-AP wt IL3, pMz-AP $\Delta$ AUIL3 and pPIL3-AP-wt IL3, which comprise either the LTR promoter or IL3 promoter, an AP reporter gene and either wild type or mutant IL3 3' UTR that comprises the mRNA instability sequence. The Examiner further contends that Banholzer discloses an expression system comprising a DNA encoding a protein having a detectable signal, as any protein would have a detectable signal as they can be detected by labeled antibody. Applicants respectfully traverse these contentions.

Present claim 4 (and hence, claims 5-7, 16 and 17 that depend ultimately therefrom, and that are also rejected over Banholzer) recites "... 2) an instability region consisting of at least 20-100 nucleotides of the 3' UTR of a gene sequence which confers instability to a mRNA , wherein the instability region is inserted into the 3' UTR of the expression cassette." Banholzer does not disclose an instability region that is *inserted* into the 3' UTR of the expression cassette. Instead, Banholzer disclose reporter gene constructs containing an AU-rich element (ARE) in the 3' UTR from IL-3 fused to the alkaline phosphatase gene, and analogous constructs from which the ARE has been removed. In generating these constructs, the entire 3' UTR of the reporter gene is removed and replaced by fusing the 3' UTR from the IL-3 to the reporter gene. Hence, Banholzer does not disclose the *insertion* of a heterologous 3' UTR into the 3' UTR of a reporter gene, as recited in the presently claimed invention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. Since Banholzer does not expressly or inherently disclose one or more elements of the presently claimed invention, this reference cannot and does not anticipate claims 4-7, 16 and 17. Therefore, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Banholzer are respectfully requested.

***VII. The Rejection Under 35 U.S.C. § 103(a) Over Banholzer and Zhang***

In the Office Action at pages 7-8, the Examiner has rejected claims 1, 3 and 15 under 35 U.S.C. § 103(a), as being unpatentable over Banholzer in view of Zhang *et al.* (*Biochem. Biophys. Res. Comm.* 227:707-711 (1996); hereinafter "Zhang"). Applicants respectfully traverse this rejection.

The Examiner correctly notes that Banholzer does *not* disclose a method of screening compounds that affect mRNA stability by using an expression system comprising a reporter gene, wherein the protein signal is measured to determine whether the test compound affects mRNA stability (*see* Office Action at page 7, third paragraph). The Examiner relies on the disclosure of Zhang to cure this serious deficiency in Banholzer, and contends that it would have been obvious to one of ordinary skill to develop a method of screening compounds that induce mRNA instability by using an expression cassette disclosed by Banholzer and further attach a GFP reporter gene. Applicants respectfully traverse these contentions.

Applicants submit that the serious deficiencies in Banzholzer are not cured by the disclosure of Zhang. Zhang does not disclose, suggest or contemplate a method of screening compounds that affect the stability of mNRA using a reporter gene DNA expression system

as recited in the presently claimed invention. Hence, Applicants respectfully submit that the ordinarily skilled artisan would not have obtained the presently claimed invention by combining these two references.

Applicants further note that the skilled artisan would not have found motivation to combine the disclosure of Banholzer with the disclosure of Zhang, as Banholzer does not disclose, suggest or contemplate the use of a reporter gene construct as disclosed in Zhang. In addition, Applicants note that Zhang does not disclose or suggest the use of the green fluorescent protein reporter gene for use in screening for compounds that induce mRNA instability. Hence, there is no disclosure or suggestion in Banholzer or Zhang that would have motivated one of ordinary skill in the art to combine these two references to make and use the presently claimed invention.

In view of the forgoing remarks, Applicants respectfully assert that the Examiner has not established a *prima facie* case of obviousness, and hence claims 1, 3 and 15 would not have been obvious over the disclosures of Banholzer and Zhang, alone or in combination. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) over Banholzer in view of Zhang therefore are respectfully requested.

***VIII. The Rejection Under 35 U.S.C. § 103(a) Over Danner in view of Maniatis***

In the Office Action at pages 8-9, the Examiner has rejected claims 8 and 9 under 35 U.S.C. § 103(a) as being unpatentable over Danner (*J. Biol. Chem.* 273:3223-3229 (1998); hereinafter "Danner") in view of Maniatis (Molecular Cloning, A Laboratory Manual, p 16.33-16.17 (1989); hereinafter "Maniatis"). Applicants respectfully traverse the rejection.

The Examiner contends that Danner discloses a cell line transfected with a wild type  $\beta$ 2AR expression vector, a  $\beta$ -globulin expression vector and a chimeric expression vector comprising  $\beta$ -globulin and 3' UTR of  $\beta$ 2AR (either with or without mRNA instability sequence). The Examiner asserts that while Danner does not disclose methods to stably transfect cells as recited in the present invention, it would have been obvious to combine the disclosure of Danner with the disclosure of Maniatis, who discloses a method to stably transfect cells.

Applicants respectfully traverse these contentions, and note that present claims 8 and 9 depend ultimately from claim 4. As noted above, claim 4 recites "... 2) an instability region consisting of at least 20-100 nucleotides of the 3' UTR of a gene sequence which confers instability to a mRNA, wherein the instability region is inserted into the 3' UTR of the expression cassette." Applicants submit that Danner does not disclose a stably transfected cell line co-transfected with an expression vector encoding a reporter gene which includes a heterologous 3' UTR that has been inserted into the 3' UTR of a reporter gene, as recited in the present invention. Applicants further submit that Danner does not disclose, suggest or contemplate a method of screening for compounds that affect the stability of mRNA, or assays designed to achieve this. These serious deficiencies in Danner are not cured by the disclosure of Maniatis, as Maniatis only discloses a method of stably transfecting cells.

Hence, Applicants submit that the disclosures of Maniatis and Danner, alone or in combination, cannot render obvious the presently claimed invention. In view of the arguments presented above, Applicants submit that the Examiner has not established a *prima*



*facie* case of obviousness, and therefore reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

***IX. The Objection to Claims 10 and 11***

In the Office Action at page 9, the Examiner has objected to claims 10 and 11 as being dependent upon a cancelled base claim. By the forgoing amendments, claims 10 and 11 have been cancelled, thus this objection has been rendered moot.

***X. Other Matters***

Applicants note that the Information Disclosure Statement 1449 Forms attached to the non-final Office Action dated August 28, 2002 (Paper No. 7) included pages 1-5 and 8-11 of the Applicants' original submission. However, pages 6 and 7 citing documents AR6-AT6 and AR7-AT7 were not received, nor were they received with the present Office Action (Paper No. 11). Applicants respectfully request that the Examiner return copies of these pages, noting that the citations were reviewed, with the next Office Action.

**XI. Conclusion**

All of the stated grounds of rejection and objection have been properly traversed or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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